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Crossmodal representation of a functional robotic hand arises after extensive training in healthy participants

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TITLE PAGE

Crossmodal representation of a functional robotic hand arises after extensive training in normal subjects

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Running head: Crossmodal representation of a robotic limb

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Abstract

The way in which humans represent their own bodies is critical in guiding their interactions with the environment. To achieve successful body-space interactions, the body representation is strictly connected with that of the space immediately surrounding it, through efficient visuotactile crossmodal integration. Such a body-space integrated representation is not fixed, but can be dynamically modulated by the use of external tools. Our study aims to explore the effect of using a complex tool, namely a functional prosthesis, on crossmodal visuo-tactile spatial interactions in healthy participants. By using the crossmodal visuo-tactile congruency paradigm, we found that a prolonged training with a mechanical hand, capable of distal hand movements and providing sensory feedback, induces a pattern of interference of visual stimuli close to the prosthesis with touches on the body. Such a pattern of interference suggests that the training ends up in an update of bodily and spatial coordinates compatible with an inclusion of the functional prosthesis in the participant's body representation. This finding adds to previous evidence for the embodiment of functional prostheses in amputees, and shows that their use may also improve the crossmodal combination of somatosensory feedback delivered by the prosthesis with visual stimuli in the space around it, thus effectively augmenting the patients' visuomotor abilities.

1. Introduction

The absence of a limb, whether acquired or congenital, dramatically limits our interactions with the outside world. In the rehabilitation of people who either underwent limb amputation or suffer from congenital limb deficiency (complete or partial absence of a limb since birth, Gold et al., 2011), the use of artificial and prosthetic limbs plays a leading role (Fraser et al., 1998). Although these technological supports are often capable of replacing some functions of the absent limb, they sometimes provide imperfect solutions (e.g., Murray, 2004).

Medical communities working with people who use prostheses often point out the need to transform the feeling relative to an artificial limb from that of an “inert supplement” or an “extracorporeal structure” into that of an incorporated, comfortable and efficient body part (Scarry, 1994). In this regard, some intriguing results have recently been obtained after the development of functional prostheses. Using the exciting technique of *targeted reinnervation* (see Kuiken, 2006, for review), patients can control the movements of a robotic prosthesis as well as receive somatosensory feedback from it, through redirected peripheral nerves that once mapped the territory of the missing limb (Kuiken, Dumanian, Lipschutz, Miller, Stubblefield, 2004). On the sensory side, a sense of touch has been implemented by using a robotic tactile interface (G10 tactor) that is connected to a skin region innervated by redirected nerves (Marasco, Kim, Colgate, Peshkin, & Kuiken, 2011). In this way, when the reinnervated skin receives any input from the prosthesis, amputees experience a sensation comparable to a realistic stimulation of the absent limb (Marasco, Schultz, & Kuiken, 2009). Moreover, the same group (Marasco, Kim, Colgate, Peshkin, & Kuiken, 2011) reported that two amputees, who underwent targeted reinnervation, had developed a sense of ownership towards the artificial supplement, as assessed by means of

several concurrent independent measures (self-report of patients' sensations during the experiments, questionnaires, psychophysical temporal order judgements, physiological temperature measurements). A very recent technical development in this line of research has been also reported by Micera (2013), whose low-invasive *intraneural electrodes* system allows amputees to re-establish a bidirectional flow of information between the subject's nervous system and the prosthetic device, thus ideally promoting the acceptance of the prosthesis itself as a body-like part.

The above evidence nicely show that an artificial limb can be felt as part of one's own body after appropriate and congruent sensory stimulation. Conversely, the lack of sensory feedback of less evolved kinds of prostheses, such as myoelectric devices, is often reported as a major drawback, which dramatically limits the usability and the acceptance of the prosthesis by the patient (see Lundborg & Rosen, 2001, for a review). Then, the capability of providing a reliable sensory feedback undoubtedly represents a major advancement towards the goal of prostheses acquiring a representation as close as possible to a regular body part. However, a complementary, yet critical proof of prostheses being represented as a real limb would be the integration of such tactile feedback information from the prosthesis with visual information available in the space surrounding the body.

A large body of evidence has shown that body representation is strictly linked with that of the space immediately surrounding it, the so-called *peripersonal space* (Fogassi, Gallese, Fadiga, Luppino, Matelli, et al., 1996), through the strong integration of multisensory input, in particular tactile stimuli on the skin and visual stimuli in the space close to the touched skin. This has been confirmed at the neural level in monkeys, by the discovery of bimodal neurons responding to tactile stimuli on a given skin region and nearby visual stimuli (Graziano, Yap, & Gross, 1994;

Graziano, 1999), as well as in humans, by means of neuroimaging studies (Macaluso & Driver, 2001; Macaluso, Frith, & Driver, 2002).

Similarly to a real limb, which shows crossmodal integration of stimuli occurring in the space immediately surrounding it, crossmodally-represented prostheses should efficiently integrate tactile input with visual stimuli occurring in their surrounding space, in order to allow optimal manipulative skills. To the best of our knowledge, however, such evidence is still lacking.

In the present study, we aim to address whether ad-hoc training with a functional prosthetic hand in normal subjects can lead to the acquisition of properties which are typical of real limbs, namely, the crossmodal combination of visuo-tactile events occurring close in space. Remarkably, this feature is strictly linked with the sense of ownership (Zopf, Savage, and Williams, 2010), as both are fundamental aspects of the representation of the body in the brain (Berlucchi & Aglioti, 1997, 2010).

At behavioral level, crossmodal spatial interference paradigms (e.g., Spence, Pavani, & Driver, 2004a) have been extensively used for the last decade to investigate interactions between vision and touch in close proximity to the body. In particular, the so-called *crossmodal congruency effect* (CCE; Driver & Spence, 1998; Spence et al., 2004a) is probably one of the most widely used measures for assessing visuo-tactile spatial interactions (Pavani, Spence & Driver, 2000; Spence, Pavani & Driver, 2004a; Spence, Pavani, Maravita & Holmes, 2004b). In this paradigm, participants perform an elevation discrimination of a tactile target delivered at the index (i.e., in a relatively “upper” position) or thumb fingers (i.e., in a relatively “lower” position), while ignoring concurrent visual distracters (see “Materials and methods” for a detailed description). It is typically found that congruent stimuli pairs (target and distracter at the same elevation) produce faster response times and higher accuracies than incongruent pairs (target and distracter at the different elevations).

The visuo-tactile interference typically observed in this paradigm is thought to be mediated by multiple components, namely, response-related factors such as conflict due to the involuntary activation of the motor response associated with the distracter on incongruent trials (Spence et al., 2004a; Shore, Barnes, & Spence, 2006; Forster & Pavone, 2008), as well as attentional and perceptual-related factors (Shore et al., 2006; Spence et al., 2004a; see also discussion in Marini, Chelazzi, & Maravita, 2012). Given that this paradigm relies on multiple mechanisms at different stages of processing of crossmodal stimuli, it is an ideal candidate for assessing the multisensory properties of the space around the body (Spence, Pavani, Maravita, & Holmes, 2004b).

Even more intriguingly, the crossmodal congruency task not only is a well-established measure for the crossmodal representation of space, but it has been also related to the sense of ownership of an external limb, as recently demonstrated by Zopf and colleagues (Zopf, Savage, and Williams, 2010). In their study, the visuo-tactile interference of CCE was examined in conjunction with another well-known visuo-tactile conflict paradigm, the so-called *rubber hand illusion* (RHI) (Botvinick & Cohen, 1998). In the RHI, normally limbed participants receive unseen touches on a hand, while observing synchronous visual strokes delivered to a rubber hand placed in front of them. Participants typically refer the sensation of touch to the location where it is *seen*, as if their real hand were shifted inside the rubber hand (see also Mulvey, Fawcner, Radford, & Johnson, 2008 for a similar illusion induced through using transcutaneous electrical nerve stimulation). Interestingly, in the study by Zopf and colleagues, a direct relationship between the rubber-hand illusion and the CCE has been established. An increase in the sense of ownership towards the rubber hand, as indexed by the magnitude of the illusion (assessed on a multi-dimensional rating-scale), was associated with a larger CCE, whilst a diminished sense of ownership after asynchronous stimulation was associated with a smaller CCE (Zopf et al., 2010).

Given the aforementioned evidence, the crossmodal congruency effect clearly represents an optimal measure to assess whether a prosthetic limb might acquire one of the most prototypical and representative feature of a real limb, i.e. the multisensory representation of its surrounding space, as a clue for its incorporation in the body representation. Differently from an alien rubber hand, however, a prosthetic limb is by far a more complex object and requires an extensive practice before participants are able to deal with it. Other differences between these two tools are even more remarkable. Whilst the rubber hand is generally only *passively* observed by participants, the prosthesis requires to be *actively* controlled and used to interact with the environment (i.e., for grasping or manipulating objects). Finally, the tactile sensation experienced by participants is also more complex when using the prosthetic limb, as compared to the rubber hand, because it implies a differentiation and a remapping of spatial positions (see below for further details). For all these reasons, it appears reasonable to expect that, differently from the rubber hand illusion which has a relatively abrupt onset, an extensive training is required and different mechanisms come to play for a prosthetic limb before it starts acquiring a multimodal representation similarly to a real limb.

In this regard, we reasoned that the process of crossmodal embodiment of the prosthetic limb might further benefit from an ecologically valid training oriented towards everyday activities, therefore we decided to use a training which includes the use of common objects and their manipulations typically performed in real-life situations. This idea nicely fits with recent evidence showing that the observation of pictures representing manipulable objects (e.g., a toothbrush), as compared to non-manipulable objects, resulted in an automatic remapping of peripersonal space (van Elk & Blanke, 2011). This may happen because the observation of a manipulable object

automatically retrieves the motor programs and body postures associated with actual object-use, thus facilitating crossmodal integration in peripersonal space.

In the present study, we measured the CCE aiming to assess whether the crossmodal representation of normally limbed participants' peripersonal space is modified after practicing in a skilful way with a robotic hand for a 4-weeks long ecologically-oriented training period (Experiment 1). The robotic hand was equipped with built-in tactile sensors, positioned on each finger and on the palm, providing the participants with tactile feedback on their arm via cutaneous electrodes. We hypothesized that, as a consequence of the motor training, the tactile stimuli delivered at the arm should start being referred to the fingers of the robotic hand where the tactile sensors were placed, in a fashion reminiscent of targeted reinnervation (Kuiken et al., 2007). This being true, then tactile stimuli delivered on the arm should show a crossmodal interference with visual stimuli delivered to the fingers of the robotic hand, as if they were actually close to the real hand of the participant. Such evidence would witness that the robotic hand has acquired multisensory competences akin to that of a real hand.

Finally, we ran a control experiment (Experiment 2), in which we shortened the training period to a single-shot session, in order to rule out the possibility that results of Experiment 1 were induced by the last training session only. Experiment 2 also allowed to test our accessory hypothesis that changes of crossmodal properties of a functional prosthesis occur at a substantially slower pace (and thus, probably, through different processes) as compared to those typically observed in the rubber hand illusion.

2. Materials and methods

2.1 Experiment 1

2.1.1 *Participants*

Eight subjects (mean age: 26.2 ± 3 , 4 females, 8 right-handed) participated in this experiment. Six of them participated in the experiment at the University of Zurich and the remaining two at University of Milano-Bicocca. All participants had normal or corrected-to-normal vision, were naïve as to the objective of the study and gave their informed consent to take part in the study. The study was approved by the ethical committees of the University of Zurich and the University of Milano-Bicocca, and it was conducted in accordance with the Declaration of Helsinki (World Medical Organization, 1996).

2.1.2 *Experimental procedure*

Experiment 1 consisted in a training period of 20 daily sessions, during which subjects learned to control the robot hand through their own muscular activity, and by a baseline pre-training and a final post-training sessions in which visuo-tactile interference was measured through the crossmodal congruency paradigm (see 2.1.4, below) in order to assess the effects of the training on crossmodal spatial integration.

2.1.3 *Robot hand Training: Apparatus and Procedure*

The robot hand was constituted by a forearm and a hand with five mechanical fingers, each one with two degrees of freedom, and it was equipped with pressure sensors on each fingertip and in

the palm, for delivering tactile feedback (Hernandez-Arieta, Kato, Yokoi, & Wenwei, 2006). The hand was controlled by means of the subject's muscular activity, hence it was interfaced with flexor digitorum superficialis muscle by means of two electrodes capturing electromyographic (EMG) signals. The calibration of the robot hand was performed at the beginning of each training session by means of a computer-based algorithm using a feed-forward neural network, with an automated procedure extracting EMG signals and then estimating parameters for clustering these signals into a classification unit. A separated supervision unit was used to control movement execution. As a result of these computational steps, the contractions of the subject's muscles resulted in a congruent movement of the robot hand, whilst muscle stretching resulted in a relaxation of the robot hand.

The pressure sensors producing the afferent signals were connected to two tactile stimulators, each one consisting of a positive and a negative electrode, positioned one above the other on the external surface of the right arm, at a distance of about 10 cm (see Figure 1). The activation of the stimulators occurred any time the fingers touched an object, and produced a subjective tactile sensation that was referred to a location in between the positive and the negative electrodes of each stimulator. With this arrangement of the stimulators participants received tactile stimulation on their right arm. The resulting sensation could be experienced on two possible locations, one above the other, depending on the stimulated fingers; the lower location corresponded to a thumb stimulation, while the upper location to the stimulation of the other fingers.

*****FIGURE 1 AROUND HERE*****

Each training session was structured as follows. The participant's right hand was always hidden below a wooden board, on top of which the robot hand rested, assuming a posture compatible to that of the hand below. After a short period of free practice, the subject was asked to use the robot hand and perform simple grasp-and-release actions with different objects, such as a ball and a can (see Figure 1). Along the training, task difficulty was progressively increased. Examples of more complex exercises are grasping and holding an object, and grasping moving objects (e.g. a ball rolling towards the hand). The final part of each training session included activities requiring a subtle control of both the robot hand and the subject's left hand, such as threading a needle, and turning the screw cap of a jar. We planned a total training duration of 30 hours after striking results of a recent target reinnervation study (Kuiken, Li, Lock, Lipschutz, Miller, et al., 2009), although we decided to extend it along four weeks (with 5 daily sessions per week, 1.5 hours each) instead of two, given that previous studies used training periods lasting up to three months (Kuiken et al., 2007).

2.1.4 Pre-training and post-training sessions: Apparatus and Procedure

The experimental apparatus for both the pre- and the post-training testing sessions consisted of a vertical panel in which two foam blocks (8 x 5 X 3 cm) were fixed to the left and the right side of a central fixation point, at a lateral distance of 20 cm.

Experimental subjects sat at a distance of 60 cm from the central fixation point. They placed their forearms on the table. With their left hand, they held the left-sided block, keeping the index finger on the upper vibrotactile stimulator and the thumb on the lower stimulator. As for the training session, the right forearm was occluded from vision by means of a horizontal panel, over which the robot hand rested. The robot hand was positioned such as it grasped the right-side foam

block, with the thumb on the bottom and the index on the upper part of the block, i.e. mimicking the spatial position of the homologous fingers of the participant's left hand. Two vibrotactile stimulators (custom-made electromagnetic solenoids, Heijo Electronics, Beckenham, UK; www.heijo.com) were embedded in the left-sided foam block, at its top and bottom external angles, thus making contact with the index finger and thumb of the left hand, respectively. Two further identical stimulators were placed on the subject's right arm, in two positions, one above the other, at a distance of about 10 centimeters. The resulting sensations corresponded exactly to the position of the referred tactile sensation induced by the electrodes during the training (see Figure 1). Four visual distracters, consisting of flashes from red light emitting diodes (LEDs), were located close to the vibrotactile stimulators on the left-sided block and in homologous high/low positions on the right-sided block. With this arrangement, a visual distracter was close to each finger of the participant's hand, on the left side, and of the robot hand, on the right side.

When switched on, vibrotactile stimulators and LEDs produced three 30 ms single pulses interleaved with two 30 ms off-phases, resulting in a total duration of 150 ms for each stimulus. The stimulus sequence was randomized. Presentation and timing of both the tactile and the visual stimuli were under computer control (through a custom-made I/O stimulator box, and E-Studio software, Psychology Software Tools, Inc., Pittsburgh, PA, www.pstnet.com).

Each testing session consisted in a tactile elevation discrimination task in a similar vein to the one previously used to investigate the crossmodal congruency effect (CCE) (Spence et al., 2004b). On each trial, subjects received one vibrotactile and one visual stimulation. Vibrotactile stimulation was randomly delivered at one out of four possible locations (left index finger, left thumb, upper right arm, lower right arm) and a simultaneous visual distracter was randomly delivered at one out of the four possible visual locations (upper left block, lower left block, upper

right block, lower right block). With this procedure, the visual distracters were equally likely to occur at a congruent or an incongruent elevation and/or at the same or different side of the targets. The orthogonal manipulation of side and elevation in this design resulted in four experimental combinations of target-distracter relative location. The distracter could be located at the same elevation and on the same side as the target (congruent-same, CS); at the same elevation, but on the opposite side (congruent-opposite, CO); at a different elevation, yet on the target side (incongruent-same, IS); at a different elevation and on the opposite side (incongruent-opposite, IO).

Participants gave speeded elevation discrimination responses to the vibrotactile targets, while ignoring the distracters. Reaction time (RT) and accuracy (Acc) of vocal responses were recorded.

2.1.4 Aim of Experiment 1

By contrasting the results of the pre-training and post-training sessions we sought to explore whether visual distracters near the robot hand started to produce a larger interference effect on the tactile targets located far away, on the arm, following a long training period in which any contact of the robot fingers (thumb versus other fingers) with the manipulated objects was systematically coupled with a spatially consistent sensation on the arm. Thus, we predicted to observe a larger CCE, on the robot hand (i.e., right) side, in the post-training session, as compared to pre-training session. By contrast, we expected to find visuo-tactile interference on the left side, close to the participant's real hand, even in the pre-training session.

2.2 Experiment 2

2.2.1 Participants

Eight new subjects (mean age: 25 ± 7.8 , 5 females) all right-handed, as assessed through self-report, were recruited at University of Milano-Bicocca. All participants had normal or corrected-to-normal vision, were naïve as to the objective of the study, and gave their informed consent to take part in the study. The study was approved by the ethical committee of the University of Milano-Bicocca and it was conducted in accordance with the Declaration of Helsinki (World Medical Organization, 1996).

2.2.2 Procedure

The design of this control experiment was identical to the one used in Experiment 1, with the only exception that subject were engaged in one training session only, of a duration of around one hour and a half, between the pre-training and the post-training testing sessions.

2.2.3 Aim of Experiment 2

The aim of this experiment was to test for any rapid adaptation effect to the robot hand on visuotactile performance. In fact, one might think that any effect found in Experiment 1 following the long training could simply be a rapidly growing effect occurring in the last session, before the post-training test, similar to those observed in bodily illusion such as the Rubber Hand Illusion (Botvinick & Cohen 1998) or occurring following different kinds of tool-use trainings (Maravita & Erika, 2004).

2.3 Analysis

RTs were filtered to eliminate outliers, i.e. responses below 150ms (anticipatory responses) or exceeding 1500ms (delayed responses). Accuracy and RT values were used to calculate the inverse efficiency (IE) score (Townsend & Ashby, 1983), which constitutes the main dependent measure of these experiments. Inverse efficiency (defined as the ratio between the mean RT and the proportion of correct responses) allows counterbalancing eventual speed-accuracy trade-offs. Since it offers a more reliable measure of performance in tasks where both speed and accuracy index performance, inverse efficiency has been extensively used in previous studies that used the crossmodal congruency paradigm (e.g., Holmes et al., 2004; Heed et al., 2010; Marini et al., 2012). In order to normalize the single-subjects data, in the correlation analysis CCE values were ipsatized by dividing the Incongruent-Congruent difference by their sum [i.e., $CCE = (Inc - Cong) / (Inc + Cong)$]. Normality and kurtosis were checked to assess the shape of the data distribution, with a threshold value of 3.

Statistical comparisons were conducted by means of repeated-measure analyses of variance (ANOVA). Two separate ANOVAs with a within-subjects 2x2x2 factorial design were conducted for each experiment. When significant effects emerged in an ANOVA, the effect size was computed by calculating the eta-squared index. Post-hoc comparisons, when appropriate, were conducted with the LSD-Fisher test. Statistical analyses were performed using Statistica for Windows, release 6.0 (StatSoft Italia SRL).

3. Results

3.1 Experiment 1

The first ANOVA aimed to evaluate the occurrence of a significant CCE, defined as the difference in IE values between incongruent and congruent conditions, on the real hand (left side) in the pre-training session. Establishing the presence of a standard CCE on is a pre-requisite in order to subsequently use it as a reliable measure of subjects' performance following the training.

In this 2x2x2 ANOVA we used as main factors: *side of the tactile target stimulus* (left, right), *relative side of the visual distracter* with respect to the target (same, opposite), and *congruency between tactile and visual stimuli* (congruent, incongruent). The main factor *congruency* turned out to be significant [$F(1,7)=10.512$, $p<.05$, $\eta^2=0.182$], with incongruent target-distracter pairs eliciting more interference than congruent pairs (mean IEs: 620 ms and 672 ms, respectively). Also the *relative side of the visual distracter* was significant as a main factor [$F(1,7)=5.697$, $p<.05$, $\eta^2=0.03$], with same side target-distracter pairs showing larger crossmodal interference than opposite side pairs. This pattern of results is that typically observed using the crossmodal congruency paradigm (Spence et al., 2004b).

*****FIGURE 2 AROUND HERE*****

The interaction between *target side* and *congruency* was significant [$F(1,7)=6.73$, $p<.05$, $\eta^2=0.051$]. Post-hoc analysis revealed that the congruency effect was observed in the pre-training session, but only for stimuli delivered to the real hand ($p<.005$), whilst visual distracters delivered

to the robot hand fingers did not elicit a significant interference with tactile targets placed on the right arm of the subject ($p=.14$) (see Figure 2). This finding is in agreement with our predictions and established that there was no link between the visual stimuli near the robot hand and the somatosensory stimuli on the arm, before the training. Finally, also the interaction between *target side* and *relative distracter side* was significant [$F(1,7)=5.981$, $p<.01$, $\eta^2=0.053$]. Subsequent post-hoc analyses showed that visuo-tactile interference was larger for same-side pairs on the real hand, compared to opposite-side pairs ($p<.05$), thus replicating the typical pattern of spatial interference found in the crossmodal congruency paradigm (Spence et al., 2004a; 2004b). By contrast, no modulation by *relative distracter side* was observed on the side pertinent to the robot hand ($p=.68$). Thus, our data definitely pinpoint the existence of a crossmodal congruency effect, on the subject real hand only, before the training.

We then analyzed the modulations of the CCE on both real and robotic hands as a result of the training by running another $2 \times 2 \times 2$ ANOVA, factoring *time of measurement* (pre-training, post-training), *side of the tactile target* stimulus (left, right), and *relative side of the distracter* with respect to the target (same, opposite). The main factor *relative side of the distracter* turned out to be significant [$F(1,7)=20.631$, $p<.005$, $\eta^2=0.17$]. A visual distracter caused larger interference when it was delivered to the same side (mean CCE: 91 ms), as compared to the opposite side (mean CCE: 30 ms) of the tactile target.

*****FIGURE 3 AROUND HERE*****

More interestingly, also the interaction between *time of measurement* and *target side* reached significance level [$F(1,7)=6.684$, $p<.05$, $\eta^2=0.039$]. Post-hoc comparisons revealed that,

before training, the crossmodal congruency effect was smaller on the right side of the body (i.e., the side of the robot hand), as compared to the left side (25 ms and 83 ms, respectively; $p < .01$). After training, this difference was virtually zero (67 ms and 66 ms, respectively; $p = .98$), due to a significant increase in the distracter interference between pre- and post-training on the right side ($p < .05$). Our results thus attest to an increased CCE measured on the robot hand side subsequently to the training (see Figure 3). It is worth noting that, in the post-training test, the distracter interference on the robot hand side had increased so dramatically that it did not differ from that found on the real hand, as measured either before ($p = .34$) or after the training ($p = .98$; Figure 3). We also reasoned that additional evidence for the development of an embodiment of the robot hand should be found when analyzing the interference effect on a per-subject basis. To this aim, we decided to run a correlation analysis, across subjects, directly comparing individual CCE values on the real hand with those on the robot hand, before and after the training, respectively. In this logic, the eventual finding of a positive correlation in CCE between real and robot hand selectively in the post-training, on a per-subject basis, would strengthen our results. The two correlation analyses showed that, across subjects, the CCE values between the two hands were uncorrelated in the pre-training session (adjusted- $R^2 = 0.03$, $p = 0.31$), whilst a significant, positive correlation in the CCE values between real and robot hand was observed in the post-training session (adjusted- $R^2 = 0.60$, $p < 0.05$) (Figure 4). Thus, the group-level findings of a comparable interference between real and robot hand in the post training session are paralleled by a compatible pattern of results also when correlating real- and robot-hand interference on a per-subject basis.

*****FIGURE 4 AROUND HERE*****

Finally, the interaction between *target side* and *relative distracter side* was significant [$F(1,7)=13.464$, $p<.01$, $\eta^2=0.118$], with left same-side target-distracter pairs eliciting the largest interference (all $ps< 0.05$). Since the *target-by-distracter side* interaction collapses pre- and post-training measures together, this result is likely driven by the fact that both pre- and post-training measures show larger interference for the real hand, in spite of the increased IE on the robot hand, which was observed only in the post-training. The three-way interaction between *time of measurement*, *target side*, and *relative distracter side* did not reach significance [$F(1,7)=1.82$, $p=.21$]. Although a post-hoc comparison cannot be accomplished under such circumstances, one can anecdotally observe that, on the robot hand side, same side target-distracter pairs elicited a slightly larger incongruence effect than opposite side pairs (70 ms and 64 ms, respectively).

3.2 Experiment 2

In analogy to the analyses performed for Experiment 1, we first tested the occurrence of a crossmodal congruency effect by running a $2 \times 2 \times 2$ ANOVA factoring *side of the tactile target stimulus* (left, right), *relative side of the visual distracter* with respect to the target (same, opposite), and *congruency between tactile and visual stimuli* (congruent, incongruent).

We observed a significant main effect of *congruency* [$F(1,7)=14.623$, $p<.01$, $\eta^2=0.14$], with congruent target-distracter pairs (mean IE: 611 ms) eliciting higher performance than incongruent pairs (mean IE: 664 ms). A significant effect was found for the interaction between *target side* and *congruency* [$F(1,7)=5.633$, $p<.05$, $\eta^2=0.027$]. Post-hoc tests showed that the highest performance was achieved when subjects received a tactile stimulation on the left side (i.e., on the real-hand)

and the elevation of the concurrent distracter was congruent, as compared to all other experimental conditions (all $p < .01$). Also the interaction between *target side* and *relative distracter side* turned out to be significant [$F(1,7)=33.7$, $p < .005$, $\eta^2=0.09$]. Post-hoc analyses revealed that the occurrence of the distracter on the same side of the target, as compared to the opposite, impaired subjects' performance when target stimuli were delivered to the left side (i.e., on the real hand) ($p < .005$). However, this effect reversed when target stimuli were delivered to the right side (i.e., on the arm whose forepart was visually replaced by the robot hand), with same-side distracters eliciting an even higher performance than opposite-side distracters ($p < .005$).

The most relevant finding arising from the analysis of the pre-training data is the empirical confirmation that a significant pre-training CCE was measured, also in Experiment 2, for the real hand only.

We then compared pre- and post-training sessions by performing a 2x2x2 ANOVA, factoring *time of measurement* (pre-training, post-training), *side of the tactile target* stimulus (left, right), and *relative side of the distracter* with respect to the target (same, opposite). We found a significant main effect of *target side* [$F(1,7)=9.107$, $p < .05$, $\eta^2=0.041$], with an overall larger crossmodal interference on the left, compared to the right, side (67 ms and 30 ms, respectively; see Figure 5). The interaction between *target side* and *relative distracter side* was significant [$F(1,7)=22.753$, $p < .005$, $\eta^2=0.351$]. Subsequent post-hoc tests revealed that, on the robot hand side, opposite-side distracters caused larger interference than same-side distracters ($p < .05$), whilst on the real hand side we observed the reversed pattern, with same-side distracters interfering more with targets than opposite-side distracters ($p < .005$).

Remarkably, and in striking contrast to Experiment 1, in Experiment 2 no significant effect involving the factor *time of measurement* was observed, neither as a main effect nor as an

interaction (Figure 5). This result fully confirms that a short motor training, immediately followed by a CCE testing session, does not lead to any change in the pattern of crossmodal effects on the side of the robot hand.

*****FIGURE 5 AROUND HERE*****

4. Discussion

The major aim of this study was to investigate whether a complex body extension, such as a functional robotic prosthesis of a limb, can be incorporated in the visuo-tactile crossmodal representation of the space near the body typical of real individual body parts (Macaluso and Maravita, 2010; Farnè, Demattè and Làdavas, 2005). The existing literature on amputees has provided solid evidence that artificial limbs feeding-back with realistic and congruent sensory stimulation can be felt as part of one's own body (Marasco et al., 2011). Upper limb amputees can experience the rubber hand illusion after the simultaneous stroking of the stump and the finger of their prostheses (Ehrsson et al., 2008), although it is not clear how the presence of a measurable RHI compares to the acquisition of a solid crossmodal representation of an artificial limb. In a recent study with limbed participants, the crossmodal congruency effect (CCE), a measure typically used to investigate interactions between tactile and visual stimuli in close proximity to the body, has been also used for studying modulations in the sense of ownership towards external body parts such as rubber hands (Zopf et al., 2010).

We hypothesized that an extensive and active training (but not a mere passive exposure) with a functional prosthetic limb by limbed participants would lead to the development of a crossmodal representation of the peri-limb visuo-tactile space, as assessed by means of the CCE, which is widely accepted as a reliable cognitive measure of crossmodal visuo-tactile interactions in peripersonal space. This was tested in normal individuals that participated either in a long (Experiment 1) or short (Experiment 2) training period using a robotic prosthetic hand for manipulating common-use objects and performing simple everyday-like actions. Behavioral

performance in the CCE was measured in each of two separate sessions, respectively before and after the training period, for either experiment.

In the pre-training session of Experiments 1 and 2 we observed a crossmodal congruency effect only for the real hand (i.e., when the target tactile stimulus was on the left). For the robotic hand (i.e., on the right side), instead, no visuo-tactile congruency effect was measured before the training, neither in Experiment 1 nor in Experiment 2. This result was expected, if one considers that tactile stimulators were placed on the subjects' right arm, thus spatially distant from the visual distracters placed on the foam cube held by the robotic hand. This result also ensures that, before the training, tactile stimuli delivered to the participants' right arm were not referred at all to the position of the fingers of the robotic hand, i.e., where visual distracters were actually presented. The pre-training results of both Experiment 1 and Experiment 2 are then consistent with our hypothesis that the mere exposure to the robotic hand does not induce any change in the CCE. Consequently, any change in CCE eventually observed after the training could not be ascribed to a simple passive exposure process, which has been documented, for example, in a situation where a pair rubber gloves is placed in a bodily-congruent position during the crossmodal congruency task (Pavani, Spence & Driver, 2000). Rather, our data from the pre-training session demonstrate that the simple visual exposure to a robotic hand, even if placed in a fully body-compatible position, does not determine the crossmodal remapping of the right-arm position towards the robotic hand fingers' positions.

Intriguingly, after the 4-week long training in Experiment 1, a significant visuo-tactile crossmodal interference emerged on the robotic hand side. The presence of a robust interference on the side of the robotic hand suggests that visual events close to the prosthesis had been included, as a result of training, in a crossmodal representation of the robot hand and its closer

space, which matched the position of the tactile-stimulating electrodes on the right arm. This crossmodal remapping was achieved after an extensive practice, which likely established a strong link between the vision of the contact between manipulated objects and robot hand fingers, and finger-specific sensory feedback on the right arm. In fact this link has a precise spatial code, since the thumb was feeding-back through the lower stimulator on the arm, whilst the other fingers (critically including the index finger used in the CCE paradigm) were feeding-back through the upper stimulator. After the training, spatial positions of the robot hand fingers were linked with corresponding spatial positions on the right arm, as indicated by the robust crossmodal interference between visual and tactile events delivered to these spatial positions.

Remarkably, the amount of crossmodal interference is strikingly similar for the robot hand side post-training, and the real hand side before training. Moreover, the correlation analyses on the CCE pre- and post-training show that a positive correlation between the real and the robot hand is found, across subjects, in the post-training session only (but not in the pre-training session). These latter findings further support the evidence that the robotic hand has acquired crossmodal properties similar to those shown by the real hand, following the training.

However, it should be noted that the crossmodal visuo-tactile interference effect observed on the right-side after the training was not modulated by the relative position of visual distracters (we only observed a non-significant 6 ms difference between same and opposite-side distracters). Although the majority of CCE studies have documented a significant same-opposite difference in the incongruency effect, a lack of spatial modulations by the side of distracter has been previously reported in a version of the crossmodal congruency paradigm which required an identity discrimination task (Holmes, Sanabria, Spence, & Calvert, 2006) and in a version of the task which used visual targets and tactile distracters (Walton & Spence, 2004).

In our study, the lack of statistically-significant evidence for a spatial modulation of the relative distracter side might be partly explained by the mechanisms on which the CCE itself relies. As agreed by several authors (Shore et al., 2006; Forster & Pavone, 2008; Spence et al., 2004a; see also discussion in Marini, Chelazzi, & Maravita, 2012), a major factor contributing to the visuo-tactile interference effect is probably a response-related competition (Eriksen & Eriksen, 1974; see also discussion in Spence et al. 2004a). Incongruent distracters can involuntarily prime the activation of an erroneous response in the stimulus-response mapping, which will compete with the correct response primed by the relevant target stimulus. The resolution of this conflict between opposite response tendencies is time-consuming and thus leads to the typical slowing-down observed in incongruent, as compared to congruent, trials (i.e., the CCE). With regard to the results of the present experiment, response competition mechanisms might have developed during the training, leading to the interference observed in the post-training session, on right-arm targets, and driven by both right and left (i.e., opposite-side) visual distracters. Critically, this interference was not observed at all in the pre-training session, thus accomplishing the idea that the position of the tactile stimuli on the right arm started being referred to the position of the hand fingers after the training. This remapping developed after a somatosensory feedback on the right arm had been repeatedly experienced, during the training, in close association with the observed movements of the robot hand fingers and the contact with manipulated objects. As a consequence of the visuomotor training, a specific spatial correspondence established between the fingers that elicited this somatosensory feedback (i.e., thumb and index fingers) and the upper right arm, where tactile sensations were actually perceived. Since the whole remapping process was driven by a visuomotor (as opposed to a purely perceptual) training, it is tempting to speculate that it could primarily rely on a neural premotor basis (e.g., Grafton, Fadiga, Arbib &

Rizzolatti, 1997), thus resulting in a reduced sensitivity for the discrimination of the relative side of the visual distracter.

After the results of Experiment 1, a potential, yet substantial, issue should be carefully considered before claiming that the acquisition of a crossmodal representation for the prosthetic hand is reached through slow-paced processes that require an extensive training period to determine a cognitively measurable effect. In the experimental design of Experiment 1, the post-training measurement of CCE was collected immediately after the last training session, thus we cannot completely rule out the possibility that the observed modulation of CCE were the result of a more transient and dynamic change in the crossmodal representation of peripersonal space merely induced by the last training session itself. In fact, without any testing along the 20 days of training, one might argue that even a single, brief practice session would have induced a similar visuo-tactile interference effect.

In order to test this possibility, in Experiment 2 we replicated the design of Experiment 1, with the sole exception that in Experiment 2 only one single training session (rather than 20 sessions) was performed. Similarly to Experiment 1, in Experiment 2 the post-training CCE session was performed immediately after the completion of the training. If the modulations of the crossmodal representation of the robotic hand, as observed in Experiment 1, were due to dynamic, rapid-onset processes, akin to those underlying the RHI, then in Experiment 2 we should have observed a CCE for right-sided targets even after a single training session.

Results of Experiment 2 clearly speak against this possibility. In fact, in Experiment 2 no difference was observed in the visuo-tactile interference effect *before* and *after* the training. It is worth noting that this null result further strengthens evidence from Experiment 1, because it rules out the possibility that the results of Experiment 1 were due to a mere residual effect of the

twentieth training session itself. Instead, our results suggest that the crossmodal representation of the robotic hand arises uniquely after a long (yet not after a short) training period. It is then likely that underlying processes, which lead to the visuo-tactile remapping of peripersonal space, occur in a sustained fashion along multiple exposure situations and thus differ, in their cognitive nature, from examples of embodiment of extracorporeal items, such as common tools (Cardinali et al., 2009; Maravita and Iriki, 2004; Farnè, Bonifazi & Làdavas, 2005), alien limbs and rubber hands (Botvinick & Cohen, 1998; Spence et al., 2004b).

Whilst the rubber hand illusion can be induced by means of a *passive* presentation of synchronous multimodal inputs, both tool- and prosthesis-use require an *active* manipulation of some extra-corporeal objects. However, the robotic hand is a far more complex and unusual device than most common tools. In fact, it delivers a spatially-selective tactile feedback, which consists in a superficial cutaneous, electrically-induced sensation, thus very differently from the deep tactile and proprioceptive feedback typically detected during a visuomotor activity related to common tool-use (Johnson-Frey, 2003). Although common tools, rubber hands and prostheses likely develop a crossmodal representation through different cognitive mechanisms, it is tempting to speculate that these mechanisms might also share some common neural substrate. Based on functional magnetic resonance imaging (fMRI) studies, common areas (anterior intraparietal sulcus and premotor cortex) have been identified that are both associated with the representation of visual stimuli in peripersonal space (Makin, Holmes & Zohary, 2007) and related to the ownership feeling for one's own hand (Ehrsson, Spence & Passingham, 2004) and to the illusory ownership sensation for an alien rubber hand (Ehrsson, Holmes & Passingham, 2005; Ehrsson, Wiech, Weiskopf, Dolan & Passingham, 2007). Then these areas could be considered as common landmarks whose activation plays a critical role in the representation of body part position, the

sense of ownership and the representation of peripersonal space (Lloyd, 2007; Makin, Holmes & Ehrsson, 2008).

The present results hold potentially relevant implications for amputated patients. The need for a sensory feeding-back prosthesis has been recently emphasized and its development is considered an impending must by experts across multiple disciplines (Micera, 2013). As demonstrated in targeted reinnervation studies, the use of fully functional and feeding-back prostheses dramatically increases the possibility that the prosthesis itself is felt as an integrated self-body part (Marasco et al., 2011). From a cognitive perspective, and complementarily to this evidence, we showed that sensory input from a robotic hand, during hand-object interactions, gives rise to substantial crossmodal interactions between the skin locations where sensory stimuli from the robot hand are referred and visual stimuli delivered in the peripersonal space. In particular, the property of visual stimuli near the robot hand of giving rise to a spatially specific visuo-tactile interference can then be considered as a landmark of the integration of the robot hand within the participant's body representation. This integration, in turn, could critically determine the efficacy of functional external prostheses as aids for individuals with missing limbs.

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Figure captions

Figure 1. The *upper panel* schematically depicts the experimental setup. The participant's left arm is positioned on a table, whilst his right arm is positioned below an opaque screen in correspondence with the robotic hand. Green diamonds indicate the position of the tactile stimulators: those on the arm (right-side), delivering tactile stimuli during the training (1: afference from fingers 2 to 5 and from the palm; 2: afference from the thumb); those on the foam cube (left-side), delivering tactile stimuli during the crossmodal congruency test (1: position of the index, 2 position of the thumb). Red circles represent visual distracters during the crossmodal congruency test. The *middle* and *lower panels* are illustrative pictures from one training session, where the subject is required to perform exercises such as passing a ball between the robotic and the real hand (middle panel), and grasping an empty can with the robotic arm (lower panel).

Figure 2. Inverse efficiency values (bars, left scale) measured in the pre-training phase of Experiment 1. The crossmodal congruency effect (i.e., difference between incongruent and congruent values) is also shown (semi-transparent diamonds, right scale). The graph shows that a robust congruency effect is present on the real hand side (i.e., left side) even before training ($p < 0.005$). In contrast, the small difference on the robot hand side (i.e., right side) is not significant ($p = 0.14$), suggesting that the mere exposure of the subject to the experimental setting before any training is not sufficient to make the robotic hand represented in his/her crossmodal peripersonal space.

Figure 3. The crossmodal congruency effect (CCE), defined as the difference in inverse efficiency values between incongruent and congruent distracter conditions, in Experiment 1. A significant interference was observed before training only on the real hand side, but not on the robot hand side. After the 20-sessions long training, the visuo-tactile interference on the robot hand side significantly increased ($p < 0.05$) up to values that did not differ from the interference measured on the real hand side ($p = 0.34$).

Figure 4. Across-subjects correlations between normalized CCE on the robot hand (on the *horizontal* axis) and on the real hand (on the *vertical* axis), for Experiment 1. Grey triangles represent individual subjects data from the pre-training session and the grey line represents the least-square fit of a linear regression model (adjusted- $R^2 = 0.03$, ns). Black circles represent individual subjects data from the post-training session and the black line represents the least-square fit of a linear regression model (adjusted- $R^2 = 0.60$, $p < 0.05$).

Figure 5. The crossmodal congruency effect (CCE), defined as the difference in inverse efficiency values between incongruent and congruent distracter conditions, in Experiment 2. A significant interference was observed before training only on the real hand side, but not on the robot hand side. After a single 90-minutes long training session, the visuo-tactile interference for stimuli on the robot hand side did not change with respect to the pre-training measurement. Differently from the long training in Experiment 1, which was effective in eliciting a crossmodal representation of the robotic hand, the single training session of Experiment 2 did not lead to any modification of the crossmodal properties of the subjects' peripersonal space.

Tables

Table 1. Summary of behavioral data. Mean CCE values (in *ms*) expressed in inverse efficiency scores (standard errors in brackets), for same and opposite side target-distracter pairs, during pre-training and post-training sessions, for Experiment 1 and Experiment 2.

Exp	Session	Real hand Same side	Real hand Opposite side	Robot hand Same side	Robot hand Opposite side
1	Pre-training	155 (46)	11 (9)	33 (20)	18 (18)
1	Post-training	106 (15)	27 (8)	70 (43)	64 (45)
2	Pre-training	171 (43)	-1 (9)	-10 (9)	76 (31)
2	Post-training	96 (22)	0 (13)	-11 (45)	64 (33)